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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/954,771	10/20/97	INGRAM P	HMV-006.11

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EXAMINER	
KAUFMAN, C	
ART UNIT	**PAPER NUMBER**
1646	15

DATE MAILED: 12/20/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	08/954,771	INGRAM ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication app ars on th cov r sh t with th corr spond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *1/25/99, 4/6/99* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,42-50,55-86,93-104 and 107-110* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *1,42-50,55-86,93-104 and 107-110* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☐ Notice of References Cited (PTO-892)
15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other:

DETAILED ACTION

The preliminary amendments filed 10/20/97, 1/25/99 and 4/06/99 have been entered.

Please Note: In an effort to enhance communication with our customers and reduce processing time, Group 1640 is running a Fax Response Pilot for Written Restriction Requirements. A dedicated Fax machine is in place to receive your responses. The Fax number is 703-305-3704. A Fax cover sheet is attached to this Office Action for your convenience. We encourage your participation in this Pilot program. If you have any questions or suggestions please contact Paula Hutzell, Supervisory Patent Examiner at Paula.Hutzell@uspto.gov or 703-308-4310. Thank you in advance for allowing us to enhance our customer service. Please limit the use of this dedicated Fax number to responses to Written Restrictions.

In view of the claims added by amendment, the restriction mailed 9/18/99 has been recast below to better address the claimed subject matter. A new election is required in response to the restriction set forth here.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1, 49, 50, 69-70, 76-78, 80-86, 93-104 and 107-110, drawn to method of modulating one or more of cell growth, differentiation and survival of a neuronal cell *in vitro* by providing a polypeptide, classified in class 514, subclass 2.

II. Claims 1, 49, 50, 69-70, 76-78, 80-86, 93-104 and 107-110, drawn to method of modulating one or more of cell growth, differentiation and survival of a neuronal cell *in vivo* by providing a polypeptide, classified in class 514, subclass 2.

III. Claims 1, 49, 50, 69-70, 76-78, 80-86, 93-104 and 107-110, drawn to method of modulating one or more of cell growth, differentiation and survival of a neuronal cell *in vitro* by providing a nucleic acid encoding a polypeptide, classified in class 514, subclass 44.

IV. Claims 1, 49, 50, 69-70, 76-78, 80-86, 93-104 and 107-110, drawn to method of modulating one or more of cell growth, differentiation and survival of a neuronal

cell *in vivo* by providing a nucleic acid encoding a polypeptide, classified in class 514, subclass 44.

V. Claims 55-58, 69-75, 79, 83 and 93, drawn to method of preventing, treating or reducing the severity of a neurodegenerative disorder *in vivo* by providing a polypeptide, classified in class 514, subclass 2.

VI. Claims 55-58, 69-75, 79, 83 and 93, drawn to method of preventing, treating or reducing the severity of a neurodegenerative disorder *in vivo* by providing a nucleic acid encoding a polypeptide, classified in class 514, subclass 44.

VII. Claims 59-70, 79, 83 and 93, drawn to method of preventing, treating or reducing the severity of an acute, subacute or chronic injury to the nervous system *in vivo* by providing a polypeptide, classified in class 514, subclass 2.

VIII. Claims 59-70, 79, 83 and 93, drawn to method of preventing, treating or reducing the severity of an acute, subacute or chronic injury to the nervous system *in vivo* by providing a nucleic acid encoding a polypeptide, classified in class 514, subclass 44.

IX. Claims 65 and 66, drawn to method of cerebral grafting of neuronal cells contacted with a polypeptide, classified in class 514, subclass 2.

X. Claims 65 and 66, drawn to method of cerebral grafting of neuronal cells contacted with a nucleic acid encoding a polypeptide, classified in class 514, subclass 44.

XI. Claims 42, 43 and 48, drawn to hedgehog polypeptide or fragment thereof, classified in class 530, subclass 350.

XII. Claims 44-47, drawn to nucleic acid encoding a hedgehog polypeptide or fragment thereof, classified in class 536, subclass 23.1.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and III are related to II and IV as patentably distinct methods of using the same product. The methods are directed to the *in vitro* and *in vivo* use of a hedgehog polypeptide of Inventions I/III and II/IV, respectively. These methods are considered to be

patentably distinct because the two methods require substantially different considerations based upon the location and circumstances of treatment. For example, the modulation of *in vivo* activity of a particular product requires consideration of the medical condition(s) which would necessitate such treatment, efficacy (including route of administration, dosage amounts, interaction with other body compounds and physiological systems), and ability to reach the cellular target. Such considerations are not required for analysis of methods for modulating product activity in a defined *in vitro* environment, which requires separate considerations with regard to obviousness and enablement including media determination, substrate, and other conditions for growth of target cells and use of the claimed method in culture. The two inventions, therefore, require divergent and burdensome searches, and are accordingly patentably distinct.

Inventions I-IV are related to the methods of Inventions V and VI as patentably distinct methods of using the same product. The methods of Inventions I-IV are directed to modulating cell growth, differentiation and/or survival in neuronal cells. The methods of Inventions V-VI are drawn to preventing, treating or reducing the severity of a neurodegenerative disorder. These methods are considered to be patentably distinct because the two groups of methods require substantially different considerations based upon what is being treated and what the cause/basis of the neurodegenerative disease is. For example, claim 56 does not require that a neuronal cell be contacted. Further, in neurodegenerative disorders, malfunction of the neurons themselves need not be the cause of their loss, so that treatment of neurons would not accomplish the method. Also, Inventions V and VI require treating a subject for neurodegenerative disease, which requires consideration of how the disorder is expressed, who is at risk for such a disease and an evaluation of symptoms as well as cause. Such considerations are not required for analysis of methods for modulating product activity as recited in Inventions I-IV. The groups of inventions, therefore, require divergent and burdensome searches, and are accordingly patentably distinct.

Inventions I-IV are related to the methods of Inventions VII and VIII as patentably distinct methods of using the same product. The methods of Inventions I-IV are directed to

modulating cell growth, differentiation and/or survival in neuronal cells. The methods of Inventions VI-VIII are drawn to preventing, treating or reducing the severity of an acute, subacute or chronic injury to the nervous system. There methods are considered to be patentably distinct because the two groups of methods require substantially different considerations based upon what is being treated and what the cause/basis of the injury is. For example, claim 59 does not require that a neuronal cell be contacted, and in nervous system injury, injury may be due to internal factors (*e.g.*, restricted blood flow) or external factors (*e.g.*, compression of a nerve), so that treatment of neurons would not necessarily accomplish the method. Further, Inventions VII and VIII require treating a subject with a nervous system injury, which requires consideration of how the injury occurred, what physiological systems it is affecting (*e.g.*, circulation, autonomic nervous system), whether it is acute or chronic, and an evaluation of symptoms as well as cause. Such considerations are not required for analysis of methods for modulating product activity as recited in Inventions I-IV. The groups of inventions, therefore, require divergent and burdensome searches, and are accordingly patentably distinct.

Inventions I-IV are related to methods of Inventions IX and X as patentably distinct methods of using the same product. The methods Inventions I-IV are directed to modulating cell growth, differentiation and/or survival in neuronal cells. Claims 65 and 66 of Inventions IX and X are drawn to methods of cerebral grafting. These dependent claims are not involved in accomplishing the method set forth in the preamble of claim 49 and do not further limit that method. The subject matter of claims 65 and 66 would require a different search from the methods of Inventions I-IV because the methods of Inventions IX-X require consideration of neuronal grafting, which includes use of particular neuronal cell types and ages, position of grafting, reasons for grafting, and desired outcome. These two groups of methods necessarily have different process steps. The groups of inventions, therefore, require divergent and burdensome searches, and are accordingly patentably distinct.

Inventions V-VI and VII-VIII are related as patentably distinct methods using the same product. The groups of methods of Inventions V-VI are drawn to preventing, treating or reducing the severity of a neurodegenerative disorder (Inventions V-VI) or acute, subacute or

chronic injury to the nervous system (Inventions VII-VIII). These methods are considered to be patentably distinct because the two groups of methods require substantially different considerations based upon what is being treated and what the cause/basis of the neurodegenerative disease is. Also, the two groups of methods are distinct, each from the other, because they are drawn to treatment of different subjects, i.e., those with a neurodegenerative disorder and those with an injury to the nervous system. The methods will necessarily require different process steps and clinical considerations, such as route of administration, cells or tissues to be treated, dosage. The groups of inventions, therefore, require divergent and burdensome searches, and are accordingly patentably distinct.

Inventions V-VI and VII-VIII, which are themselves distinct, are related as patentably distinct methods to Inventions IX-X as using the same product. The groups of methods of Inventions V-VI are drawn to preventing, treating or reducing the severity of a neurodegenerative disorder (Inventions V-VI) or acute, subacute or chronic injury to the nervous system (Inventions VII-VIII). Inventions IX and X are drawn to methods of cerebral grafting. While cerebral grafting might be useable for treating a neurodegenerative disorder and potentially an injury to the nervous system, the method can be used for of other than treatment of a neurodegenerative disorder or injury to the nervous system, such as in increasing neurotransmitter release for a non-disease related purpose, *e.g.*, for congenital depression, or to promote survival of co-grafted cells. Cerebral grafting requires substantially different considerations based on reasons for grafting, what cell type and age are being used, position and extent of the graft, and desired outcome. The groups of inventions, therefore, require divergent and burdensome searches, and are accordingly patentably distinct.

Inventions I, II, V, VII, IX and III, IV, VI, VIII and X are related by virtue of the methods comprising providing a hedgehog polypeptide. While each of the inventions within the two groups are distinct one from another for the reasons set forth above, the two groups of Inventions are distinct because the first group of Inventions is drawn to methods requiring the polypeptide itself (*i.e.*, administration.introduction of the polypeptide directly), whereas the second group of Inventions is drawn to methods requiring a nucleic acid encoding the

polypeptide wherein expression of the nucleic acid leads to production and the presence of the polypeptide (*i.e.,* transfection of cells or gene therapy). Each of the two groups of methods requires different process steps and considerations for administration and use. Therefore, the Inventions requiring only the polypeptide and Inventions requiring a nucleic acid encoding the polypeptide require divergent and burdensome searches, and are according patentably distinct.

Inventions XI and Inventions I, II, V, VII, IX, which are themselves distinct, are related as product and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product can be used in another materially different process such as in the production of an antibody or purification of the naturally occurring protein to which it binds.

The polypeptide of Invention XI is related to the methods of Inventions III, IV, VI, VIII and X, which are themselves distinct, by virtue of being encoded by the nucleic acid required for those methods. The inventions are distinct, however, because the encoded polypeptide can be produced by another materially different method than expression of the nucleic acid, such as by chemical synthesis. Additionally, the encoding nucleic acid can be use for a process other than encoding the polypeptide, such as in Northern analysis for transcript localization.

The nucleic acids of Invention XII is related to the methods of Inventions I, II, V, VII, IX, which are themselves distinct, by virtue of encoding the polypeptide which can be used in the method. The inventions are distinct, however, because the encoded polypeptide can be produced by another materially different method than by expression of the nucleic acid, such as by chemical synthesis. Additionally, the nucleic acid can be used for another materially different process as stated in the preceding paragraph and the encoding nucleic acid can be use for a process other than encoding the polypeptide, such as in Northern analysis for transcript localization.

Inventions XII and Inventions III, IV, VI, VIII and X, which are themselves distinct, are related as product and processes of use. The inventions can be shown to be distinct if either or

both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product can be used in another materially different process such as in in Northern analysis for transcript localization or in clonal library screening to detect structurally related nucleic acids.

The nucleic acids of Invention XII are related to the polypeptides of Invention XI by virtue of encoding the same. The nucleic acid molecule has utility for the recombinant production of the protein in a host cell. Although the nucleic acid molecule and protein are related since the nucleic acid encodes the specifically claimed protein, they are distinct inventions because the protein product can be made by another and materially different process, such as by chemical synthesis or purification from the natural source. Further, the nucleic acid may be used for processes other than the production of the protein, such as in nucleic acid library screening.

Because these inventions are distinct for the reasons given above, have recognized divergent subject matter, and because each invention requires a separate non-coextensive search, restriction for examination purposes as indicated is proper.

Claims 42, 43 and 48 of Invention XI and Claims 1, 49, 50, 69-70, 76-78, 80-86, 93-104 and 107-110 of Inventions I-II encompass a plurality of disclosed patentably distinct species comprising Sonic *hedgehog* (hh) amino sequences (SEQ ID NO:8 and 11-13), Indian hh sequences (SEQ ID NO:10 and 14) and Desert hh sequences (SEQ ID NO:9). Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

Claims 44-47 of Invention XII and Claims 1, 49, 50, 69-70, 76-78, 80-86, 93-104 and 107-110 of Inventions III-IV encompass a plurality of disclosed patentably distinct species comprising Sonic *hedgehog* (hh) nucleic acid sequences (SEQ ID NO:1 and 4-6), Indian hh sequences (SEQ ID NO:3 and 7) and Desert hh sequences (SEQ ID NO:2). Applicant is required

under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

It is noted that the Sonic, Indian and Desert subfamilies of *hedgehog* proteins have different sequences and different expression patterns (p. 19, lines 19-26 of the specification). Also, they are encoded by distinct chromosomal genes (Figure 16). If Applicants elect one of Invention I-IV, XI or XII, a specific species as set forth above should be elected in addition, with a nucleic acid species elected for III, IV or XII and a polypeptide species elected for I, II or XI.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

It is noted that claim 79 cannot further limit claim 1 upon which it ultimately depends. There is no method of treatment in claim 1 or dependent claim 78. As a result, the method of claim 79, drawn to a method of treating which repairs central or peripheral nerve damage has been restricted as it relates to Inventions V-VIII. If this designation is not appropriate, Applicants should indicate with which Invention claim 79 properly belongs.

Applicants traversal of the previous restriction requirements is still pertinent and is addressed here:

Applicant's traversal of Groups I and II (now groups I-IV and XI) of the previous restriction in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the search and examination of the entire application can be made without serious burden. This is not found persuasive because as set forth in the restriction (paper #6) the inventions are differently classified and the polypeptide can be used for materially different methods such as production of an antibody or purification of a binding protein. The search for Group II does not require a search for Group I.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Friday from 8:00AM to 4:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Claire M. Kaufman

Patent Examiner, Art Unit 1646

December 16, 1999

RESTRICTION ELECTION FACSIMILE TRANSMISSION

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